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PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Serial No. : 09/926,712)
Filed : 06 December 2001) Group Art Unit:
For : Serine Protease Inhibitors) 1625
Docket No. : 00111/US1)
Examiner: Aulakh, Charanjit

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INFORMATION DISCLOSURE STATEMENT

Assistant Commissioner for Patents
US Patent & Trademark Office
2011 South Clark Place
Customer Window, Mail Stop Patent Response
Crystal Plaza Two, Lobby, Room 1B03
UNITED STATES

Sir:

Telephone Communications with the Examiner

The undersigned left a voice mail message for the Examiner on March 11, 2003 indicating that he was preparing an Information Disclosure Statement and also intended to submit additional claims directed to methods of use of the claimed compounds. These methods of use are presently claimed in co-pending application Serial No. 09/926,716, which is intended to be abandoned. On May 6, 2003 the undersigned telephoned the Examiner to apologize for the delay in submitting the Information Disclosure Statement, and informed the Examiner that the Applicants will not be seeking to introduce method of use claims at this time. Applicants reserve the right to pursue claims to methods of use at a later date.

Background Information

This application is part of an international portfolio of patent applications protecting serine protease inhibitors, all of which are in the care of the undersigned. Some of these applications now belong to Tularik Limited, a subsidiary of Tularik Inc in South San Francisco, and some of them now belong to Eli Lilly and Company in Indianapolis. The history of all of these applications traces back to a research project on serine protease inhibitors started by a small company in the undersigned's home town, Macclesfield, U.K., known as Proteus (later Protherics) Molecular Design Limited. The original applications encompassed benzamidine and aminoisoquinoline compounds, and now belong to Tularik Limited. As the research effort has continued and involved researchers at other sites, two different directions have been followed. One direction has led to compounds that are selective for the serine protease, tryptase. These compounds generally possess an aminomethylphenyl group (corresponding

with R_2 in formula (I)), and are protected by Tularik applications. The other direction has led to further compounds that are selective for the serine protease, Factor Xa. These compounds are protected by Lilly applications. The claims in the Lilly applications have generally been drafted so that aminomethylphenyl compounds are not covered. Thus, all but one contain a proviso excluding aminoalkyl-substituted compounds (The Examiner is referred to the definition of R_1 in Claims 1 and 29 of the present application). The one exception, Serial No. 09/926,716, which contains generic method claims reading on both aminomethylphenyl and non-aminomethylphenyl compounds, is intended to be abandoned.

In order to assist the Examiner to have a complete picture of the portfolio, a listing of all co-pending U.S. applications and patents in the portfolio is attached. When the Examiner inspects these co-pending applications, the Examiner will note that in the more recent applications, including the present application, the claimed inventions are further distinguished one from another by the definitions of the group $L-Lp(D)_n$.

Thus, the first applications filed in the portfolio were WO 99/11657 and WO 99/11658, directed to aminoisoquinoline and benzamidine compounds. Serial number 09/988,082, is a continuation-in-part of WO 99/11658, and also of WO 00/77027, as described below.

Next came three PCT applications, all filed on the same day and claiming priority back to common priority documents: WO 00/76971 (of which the present application is the national stage), WO 00/77027 and WO 00/76970. WO 00/77027 claimed aminomethylphenyl compounds. It has not entered the national stage, but as described above, serial number 09/988,082 is a continuation-in-part of this application. WO 00/76971 claimed compounds which do not have an aminomethylphenyl group (see the proviso in the definition of

R₁) nor an aminoisoquinoline group (see the proviso in the definition of R₂). WO 00/76970 contained method of use claims reading on the compounds of WO 00/77027 and WO 00/76971. It has entered the national stage as serial number 09/926,716 and has been allowed, but is intended to be abandoned.

Next came four more PCT applications: WO 01/96303, WO 01/96304, WO 01/96323 and WO 01/96296, all claiming priority back to WO 00/76971. The Examiner will note from the file for the present application, that the claims have been amended in the application so as to exclude the compounds now claimed in these four co-pending applications.

Two further PCT applications were also filed and have entered the national stage: WO 01/44226 and WO 01/96305. These claim aminomethylphenyl compounds, and claim priority back to WO 00/77027.

Thus, having regard to the definitions of R₂ and Lp in Claim 1 of the present application, and in particular to the proviso excluding compounds in which R₂ is aminoisoquinolyl and the proviso excluding compounds in which R₁ is aminoalkyl, it is believed that the claims in the present application are distinguished from the claims in the other Tularik and Lilly patents and applications.

Effective from December 15, 1999, the rights in the present application, including the rights arising in the priority applications, were subject to an obligation to assign to Lilly, according to a contract executed by Protherics Molecular Design Limited and Eli Lilly and Company on that date.

Information Disclosure Statement

As a means of complying with the duty of disclosure, Applicant's submit an "Information Disclosure Statement by Applicant" on PTO Form PTO/SB/08A for consideration by the Examiner. Since this statement is being submitted during the

period specified in 37 C.F.R. § 1.97(b), it is believed that no fee is due for this submission. However, should an Office Action on the merits have been mailed, please charge Deposit Account No. 50-1230 in the amount of the fee under 37 C.F.R. § 1.17(p), and consider the information under 37 C.F.R. § 1.97(c).

It is understood that the Examiner has received a copy of the International Search Report and copies of the documents cited therein (documents A1 and B1-B7). If this is incorrect, the Examiner is kindly requested to contact the undersigned to request copies.

Applicants would like to draw the Examiner's attention to the following points relating to certain of the cited documents:

WO 99/11657 (B1), WO 99/11658 (B2) and WO 98/47876 (B3) variously disclose compounds corresponding to formula (I) in which R₂ or Lp comprises a benzamidine, aminoisoquinoline or dihydroaminoisoquinoline group. WO 99/11658 (B2) also specifically discloses, as intermediates to benzamidines, certain compounds corresponding to formula (I) in which R₂ is phenyl substituted by cyano. See Examples 88, 150, 152, 153 and 186, which correspond with compounds of formula (I) in which Lp is 4-aminomethylcyclohexyl (88, 152) or 4-methylphenyl (150, 153, 186). Applicants have not yet amended Claim 1 to distinguish it from these examples, because there may be co-pending applications by Cor Therapeutics, Inc also disclosing and claiming nitrile compounds (see under "International Applications That May Have U.S. Counterparts" below).

US 5,346,907 (A1) discloses, in Examples 61 and 62, compounds corresponding to formula (I) in which Lp is 2-propylpiperidinyl. Present Claims 1 and 29 do not read on these specific compounds. WO 91/00725 (B8) is of the same

family as US 5,346,907 (A1), but includes a broader disclosure.

WO 99/25686 (B9) discloses, as compound 2099, a compound corresponding to formula (I) in which Lp is 1-(4-chlorobenzyl)piperidin-4-yl. Present Claims 1 and 29 do not read on this compound.

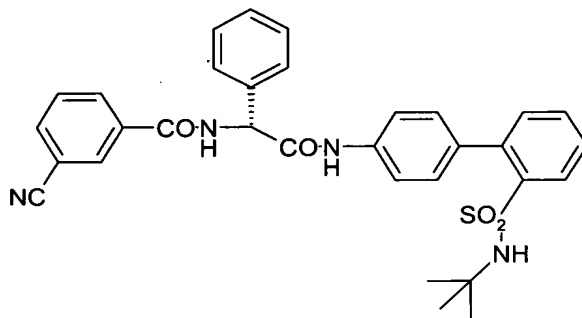
Documents B15 to B18 were published after the international filing date of the present application. They are not believed to be available as references under 35 U.S.C. 102(e).

EP 623,596 (B23), EP 648,780 (B24), EP 686,642 (B25), US 5,583,146 (A4), EP 796,866 (B26) and WO 97/49404 (B27) disclose N-acyl pyrrolidines and N-acyl piperidines as thrombin inhibitors, and intermediates useful in their preparation. The definitions of the N-acyl group may overlap, generically, with the definition of $R_2-X-X-Y(Cy)-$ in Claim 1 of the present application. The Examiner's attention is drawn in particular to EP 623,596 (B23): page 15, intermediate amine resulting from reduction of azide XIX, page 21, intermediate aldehyde XXXII, page 22, intermediate alcohol XXXIV, page 23, intermediate aldehyde XXXV, page 24, intermediate amine 24; EP 648,780 (B24): page 7, intermediate II; EP 686,642 (B25): page 14, intermediate ester IV and acid V; US 5,583,146 (A4): Column 45, intermediate amine from reduction of azide XIXa, Column 50, intermediate aldehyde XXXIIa, column 52, intermediate XXXVIIa, Column 59, line 50 intermediate acid; EP 796,866 (B26): page 9, intermediate acid II; and WO 97/49404 (B27): page 13, intermediate acid II.

Documents B28 to B31 were all published after the filing date after the international filing date of the present application. They are not believed to be available as references under 35 U.S.C. 102(e). However, they may contain U.S. counterparts.

The Cor Therapeutics, Inc applications (B29 to B31) were filed on 24 May, 2000 and claim priority from one of four U.S. provisional applications filed on 24 May, 1999.

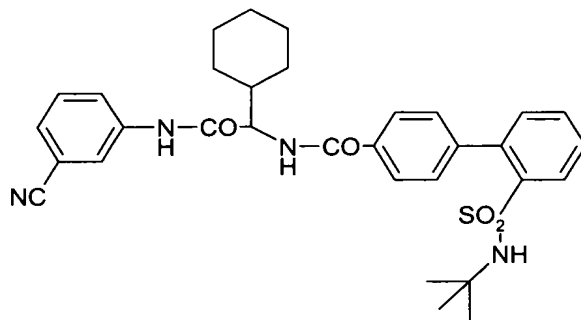
WO 00/71493 exemplifies, as an intermediate:



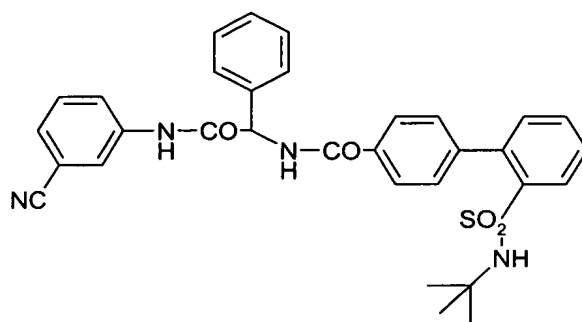
Example 25

which falls within the scope of Claim 1. This compound is also exemplified in the priority document (60/135,820) and as Example 16 in WO 00/71507. The Examiner will appreciate that this compound corresponds to formula (I) in which R_2 is phenyl substituted at the 3-position by a cyano group, and Lp is a biphenyl group substituted on the phenyl portion by a group R_3 which is ortho-t-butylaminosulphonyl (an alkylaminosulfonyl group).

WO 00/71508 exemplifies, as intermediates:



Example 34



Example 35.

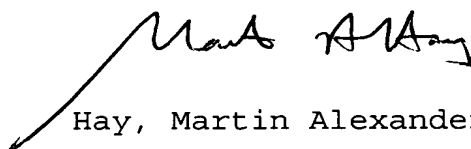
The Examiner is referred to Example 33, to which Examples 34 and 35 refer. The Examiner will appreciate that these compounds corresponds to formula (I) in which R₂ is phenyl substituted at the 3-position by a cyano group, and Lp is a biphenyl group substituted on the phenyl portion by a group R₃ which is ortho-t-butylaminosulphonyl (an alkylaminosulfonyl group).

Conclusions

Product Claims 29 to 41 are believed to be allowable.

Claim 1 reads on nitrile compounds exemplified as intermediates in WO 99/11578, which is a prior publication. It also reads on nitrile compounds exemplified as intermediates in WO 00/71493, WO 00/71507 and WO 00/71508, which are not prior publications but which may have U.S. counterpart applications.

Respectfully submitted,



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Co-Pending Lilly and Tularik Applications and Patents

Co-pending Applications Assigned to Eli Lilly and Company

09/926,716 (national stage of WO 00/76970), filed 06 Dec 2001
10/030,186 (national stage of WO 01/96304), filed 04 Feb 2002
10/030,187 (national stage of WO 01/96323), filed 04 Feb 2002
10/030,188 (national stage of WO 01/96303), filed 04 Feb 2002
10/030,189 (national stage of WO 01/96296), filed 04 Feb 2002

Remarks:

It is presently intended that co-pending application serial number 09/926,716 will be abandoned, but Applicants reserve the right to introduce method of use claims into the present application.

Co-pending applications serial nos. 10/030,186 to 10/030,189 claim priority under 35 U.S.C. § 119 from PCT/GB00/02302 (WO 00/76971), of which the present application is the national stage.

On national stage entry, Applicant presented an amended set of compound claims that was drafted to avoid double patenting with the compound claims of these co-pending applications.

Co-pending Applications and Patents Assigned to Tularik Limited

US 6262069 and US 6420438 (national stage of WO 99/11657 and continuation thereof)

09/988,082, filed 19 November, 2001 as a continuation-in-part of WO 00/77027) and of Serial No. 09/485,678 (allowed then abandoned), which was the national stage of WO 99/11658).

Serial No. 09/926,712

10/148,174 (national stage of WO 01/44226), filed Dec 13, 2002
10/296,245 (national stage of WO 01/96305), filed Jun 12, 2001

Remarks:

09/988,082 claims compounds corresponding to formula (I) in present Claims 1 and 29 in which R₂ is phenyl bearing an unsubstituted or substituted amidino or aminomethyl group.

The definition of possible substituents on a phenyl R₂ group does not include these groups. The Examiner's attention is drawn in particular to the definition of R₁ and to the limitation that the group R₁ cannot be an unsubstituted aminoalkyl group. For completeness, it is pointed out that the claims in co-pending Lilly application 09/926,716, which is to be abandoned, do not include this limitation.

Co-pending applications serial numbers 10/148,174 and 10/296,245 claim compounds that are selective for the serine protease tryptase. The compounds correspond to formula (I) in the present application in which R₂ is phenyl substituted by aminomethylphenyl. Such compounds fall outside the scope of Claims 1 and 29 by virtue of the limitation that R₁ cannot be unsubstituted aminoalkyl. The compounds of the present application are selective for the serine protease Factor Xa.

